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09/508892
PCT/EP 98/05720
REC'D 18 NOV 1998
WIPO PCT

The Patent Office

The Patent Office
Concept House
Cardiff Road
Newport
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NP9 1RH

# PRIORITY DOCUMENT

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I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

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Signed Andrew Gersey

Dated 15 June 1998

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PCS9455JRH-PROV2

**9810143.9**

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*Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071-438 4700).*

*Rule 16 of the Patents Rules 1990 is the main rule governing the completion and filing of this form.*

*2 Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.*

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The Patent Office

# Request for grant of a Patent

## Form 1/77

Patents Act 1977

## 1 Title of invention

1 Please give the title of the invention

PARASITICIDAL FORMULATIONS

## 2 Applicant's details

☐ First or only applicant

2a If you are applying as a corporate body please give:

Corporate name
PFIZER LIMITED

Country *(and State of incorporation, if appropriate)*
UNITED KINGDOM

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases,** please give the following details:

Address
RAMSGATE ROAD,
SANDWICH, KENT,

UK postcode CT13 9NJ
*(if applicable)*

Country UNITED KINGDOM

ADP number
*(if known)* 6851267[illegible]

*2d, 2e and 2f:*
*If there are further applicants please provide details on a separate sheet of paper.*

☐ **Second applicant (if any)**

2d If you are applying as a corporate body please give:

Corporate name

Country *(and State of incorporation, if appropriate)*

2e If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2f **In all cases,** please give the following details:

Address

UK postcode
*(if applicable)*

Country

ADP number
*(if known)*

**3**
*An address for service in the United Kingdom must be supplied.*

*Please mark correct box*

## 3 Address for service details

3a Have you appointed an agent to deal with your application?

Yes [X] No [ ] ➡ *go to 3b*

⬇ *Please give details below*

Agent's name
MR J.R. HAYLES
Agent's address
PFIZER LIMITED
RAMSGATE ROAD
SANDWICH
KENT
Postcode CT13 9NJ

Agent's ADP number 6409593002

*3b:*
*If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.*

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

Address

Postcode

Daytime telephone number *(if available)*

ADP number
*(if known)*

## 4 Reference number

4 Agent's or applicant's reference number *(if applicable)* PCS9455JRH-PROV2

## 5 Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

*Please mark correct box*

Yes ☐ No ☒ ➡ *go to 6*

⬇ *please give details below*

☐ number of earlier application or patent number

☐ filing date *(day month year)*

☐ and the Section of the Patents Act 1977 under which you are claiming:

*Please mark correct box*

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

## 6 Declaration of priority

**6**

*If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.*

*Please give the date in all number format, for example, 31/05/90 for 31 May 1990.*

6 If you are declaring priority from previous application(s), please give:

| Country of filing | Priority application number *(if known)* | Filing date *(day,month,year)* |
|---|---|---|
| | | |

**7**

*The answer must be 'No' if:*
*- any applicant is not an inventor*
*- there is an inventor who is not an applicant, or*
*- any applicant is a corporate body.*

## 7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

*Please mark the correct box*

Yes ☐ No ☒ ➡

***A statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).***

**8**

*Please supply duplicates of claim(s), abstract, description and drawing(s).*

## 8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

| | | | |
|---|---|---|---|
| Continuation sheets for this Patents Form 1/77 | | | |
| Claim(s) | 2 | Description | 8 |
| Abstract | | Drawing(s) | 2 +2 |

8b Which of the following documents also accompanies the application?

*Please mark correct box(es)*

| | |
|---|---|
| Priority documents *(please state how many)* | |
| Translation(s) of Priority documents *(please state how many)* | |
| Patents Form 7/77 - Statement of Inventorship and Right to Grant *(please state how many)* | |
| Patents Form 9/77 - Preliminary Examination/Search | |
| Patents Form 10/77 - Request for Substantive Examination | |

**9**

*You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.*

## 9 Request

I/We request the grant of a patent on the basis of this application.

***Please sign here*** ➡

Signed [signature] pp J.R. HAYLES

Date 12/05/1998 *(day month year)*

*A completed fee sheet should preferably accompany the fee.*

***Please return the completed form, attachments and duplicates where requested, together with the prescribed fee to:***

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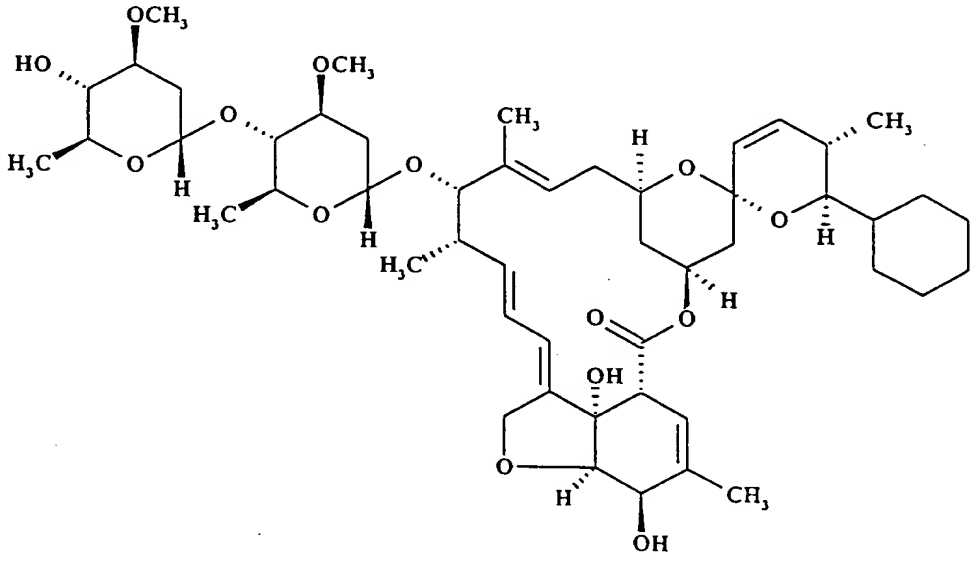
**Parasiticidal formulations**

This invention relates to a solid implant containing a parasiticidal compound having low aqueous solubility, which is particularly useful for administration to livestock such as cattle, pigs and sheep.

A number of potent macrocyclic parasiticidal compounds are known, including the avermectins and milbemycins. UK Patent N° 1,573,955 discloses a family of avermectin compounds (including avermectins B1a and B1b) which are indicated as parasiticides.

22,23-Dihydroavermectin B1 (ivermectin, disclosed in EP 1689) is available commercially in an injectable formulation (sold as IVOMEC™). Ivermectin is a mixture of at least 80% 22,23-dihydroavermectin B1a (having a 25-sec butyl group) and not more than 20% of 22,23-dihydroavermectin B1b (having a 25-isopropyl group).

25-Cyclohexyl-avermectin B1 (doramectin, disclosed in EP 214731) has the following structure,




and is available commercially in an oil formulation for injection (sold as DECTOMAX™) for the treatment and prevention of internal and external parasite infestations in cattle. The oil formulation is described in European Patent N° 393890.

The milbemycins are similar in structure to the avermectins, except that they are unsubstituted at the 13-position.

Although formulations such as DECTOMAX™ have been successful, there is a need for further formulations which are convenient to administer and which provide prolonged protection against parasites.

Thus, according to the present invention, there is provided a solid implant comprising at least one parasiticidal compound having low aqueous solubility; and tabletting excipients including a bulking agent.

Implants according to the invention may be implanted intramuscularly. Preferably however, they are implanted subcutaneously (i.e. into the fatty tissue directly below the skin).

Suitable parasiticidal compounds are those having an aqueous solubility below 100 μg/ml, for example the avermectins and milbemycins. Doramectin is of particular interest (which has an aqueous solubility of 0.6 μg/ml at pH 7). Ivermectin is also of interest.

Preferably, the bulking agent is lactose. Other suitable bulking agents include other sugars, microcrystalline cellulose (which is available commercially as AVICEL™) and dicalcium phosphate.

Other tabletting excipients which may be present include magnesium stearate, which acts as a lubricant to facilitate tabletting. Typically, magnesium stearate will make up about 3% of the implant, by weight. Binding agents may also be included in the formulation to aid granulation and compressibility. Examples of binding agents include starch, gelatin and polyvinyl pyrrolidone. Typically, the binding agent, when present, will make up between 2 to 10% of the implant, by weight.

A further tabletting excipient which the implants of the invention may optionally contain is a tablet disintegrant. Suitable tablet disintegrants include sodium starch glycolate, which

is available commercially as EXPLOTAB™. Other disintegrants which may be mentioned are dicalcium phosphate and cross-linked starch. Typically, the disintegrant, when present, will make up about 5% of the implant, by weight.

Preferably, the parasiticidal compound (or compounds) makes up between 10 and 60% of the implant, by weight, more preferably from 20 to 45% of the implant, by weight, for example 40%.

Preferably, the implants of the invention contain an antioxidant or a reducing agent. It has been found that such additives reduce or eliminate degradation of the parasiticidal compound, thus extending the shelf-life of the implant. It has been found that such additives are particularly useful for stabilizing the parasiticidal compound when the implant is sterilized by irradiation, such as gamma or beta irradiation.

Antioxidants of particular interest are butylated hydroxy anisole (BHA; a mixture of 2-*tert*-butyl-4-methoxyphenol and 3-*tert*-butyl-4-methoxyphenol) and butylated hydroxy toluene (BHT; 2,6-di-*tert*-butyl-4-methylphenol). Other antioxidants and reducing agents include alpha-tocopherol, alkyl gallate derivatives, nordihydroguaiaretic acid, ascorbic acid, sodium metabisulphate and sodium sulphite. Typically, the antioxidant, when present, will make up between 0.01 to 0.5% of the implant, by weight, more preferably 0.1 to 0.2%.

As mentioned above, the implants of the invention may be irradiated to sterilize them, typically at a dose in the range 15-25 kGy (kilo Gray).

The implants of the invention may be implanted in various parts of the animal to be treated, for example the flank, the base of the tail or the ear. Where the ears are removed during a meat rendering process, this is a preferred site for implantation.

To facilitate such implantation, the implants are preferably rod-shaped, and can be implanted conveniently using a conventional hand-operated implant gun. Suitably, rod-shaped implants are 2 to 30 mm in length, and 2 to 5 mm in diameter. Preferred

dimensions are 5 to 6 mm in length, and 2 to 3 mm in diameter. Preferably, the cross section is circular.

According to the invention, there is also provided a method for the treatment or prevention of parasitic infections which comprises administering an implant as defined above to an animal in need of such treatment.

Parasitic infections of particular interest are those caused by endoparasites including helminthiasis (most frequently caused by nematode worms in the gastrointestinal tract). The implants are also useful in treatment or prevention of ectoparasite infections such as of ticks, mites, lice, fleas, blowfly, biting insects and migrating dipterous larvae.

The dosage to be administered will depend on the animal to be treated, the parasiticidal compound being used, and the condition to be treated. However, a suitable dose of doramectin is 0.5 mg/kg of animal body weight. Typically, an implant according to the invention having the preferred dimensions mentioned above will contain about 10 mg of doramectin. Thus, for cattle weighing 120 kg, 6 implants will be needed. This provides sustained release of doramectin for up to 26 weeks. Where multiple implants are required, these can often be implanted consecutively by a single actuation of an implant gun.

The implants of the invention may be prepared by dry- or wet-mass granulation followed by milling and compression into the desired shape using conventional techniques.

The duration of action of the implants of the invention may be determined by measuring blood plasma levels in cattle following implantation. These levels have been correlated with antiparasitic activity of the compounds which have established that for effective control of helminths a blood plasma level of about 2 ng/ml needs to be maintained, and that for effective control of single-host ticks a blood plasma level of about 5 ng/ml needs to be maintained.

In a broader aspect, the invention further provides use of an antioxidant or a reducing agent in a composition containing an avermectin or a milbemycin for preventing degradation of

the avermectin or milbemycin. Although BHA has been used previously in association with doramectin in DECTOMAX™, its function was to prevent rancidity of the oil formulation rather than to aid the stability of doramectin in solution. This aspect of the invention is particularly useful when the formulation is irradiated, and may be used in liquid and non-liquid formulations (such as solids and powders).

The invention is illustrated by the following examples, and the accompanying Figures in which:

Figure 1 shows the blood plasma levels in cattle achieved by the implants prepared in Examples 1 and 2; and

Figure 2 shows the degradation profiles of implants prepared in Example 4.

Example 1

Doramectin implant

| Components | Specification | mg/unit | % by weight |
|---|---|---|---|
| Doramectin[a] | Pfizer | 10.000 | 40 |
| β-anhydrous lactose | Ph Eur | 14.250 | 57 |
| Magnesium stearate | Ph Eur | 0.750 | 3 |
| **Total** | | **25.000** | **100** |

[a] mean particle size 19.27 μm (volume mean diameter)

The components, except magnesium stearate, were blended together in a blender for 15 minutes. The blend was then sieved through a 680 μm mesh screen and blended for a further 15 minutes. After that, half of the magnesium stearate was added and blending continued for 5 minutes, after which the blend was compressed to form "slugs". The slugs were then milled to form granules, and the size fraction 250-355 μm was collected.

The collected granules were then blended for 15 minutes, and then the remaining half of the magnesium stearate was added and blending continued for 5 minutes. The blend was

then compressed on a suitable tablet machine using 2 mm tooling to produce rod-shaped implants of 2 mm diameter and 5 mm length.

Example 2

Doramectin implant containing a tablet disintegrant

| Components | Specification | mg/unit | % by weight |
|---|---|---|---|
| Doramectin[a] | Pfizer | 10.000 | 40 |
| β-anhydrous lactose | Ph Eur | 13.000 | 52 |
| Sodium starch glycolate (EXPLOTAB™) | BP | 1.250 | 5 |
| Magnesium stearate | Ph Eur | 0.750 | 3 |
| **Total** | | **25.000** | **100** |

[a] mean particle size 19.27 μm (volume mean diameter)

The implants were prepared by the method of Example 1.

Example 3

Pharmacokinetic profiling

The implants of Examples 1 and 2 were implanted into 16 cows at a dose of 500μg/kg. The blood plasma concentrations of doramectin following implantation were measured, and the results are shown in Figure 1. It can be seen that in each case single-host tick activity was obtained for more than 50 days, and control of helminths was obtained for about 90 days.

Example 4

Doramectin implant containing an antioxidant

| Components | Specification | mg/unit | % by weight |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Doramectin[a] | Pfizer | 10.000 | 40 |
| β-anhydrous lactose | Ph Eur | 11.625 | 46.5 |
| Sodium starch glycolate (EXPLOTAB™) | BP | 1.250 | 5 |
| Butylated hydroxy anisole | Ph Eur | 0.125 | 0.5 |
| Polyvinyl pyrrolidone | Ph Eur | 1.250 | 5 |
| Magnesium stearate | Ph Eur | 0.750 | 3 |
| **Total** | | **25.000** | **100** |

The components, except magnesium stearate, butylated hydroxy anisole and polyvinyl pyrrolidone, were blended together in a blender for 15 minutes. The blend was then sieved through a 680 μm mesh screen and blended for a further 15 minutes. After that, the butylated hydroxy anisole and polyvinyl pyrrolidone was dissolved in ethanol to form the granulation fluid. The volume of ethanol used was approximately 20%, by volume, of the total formulation. The granulation fluid was sprayed onto the blend under constant mixing over 10 minutes. The resultant wet granule mass was sieved through a 1.4 mm mesh screen and allowed to dry under vacuum for 3 hours at 50°C. The dried granules were then milled, and the size fraction 250-355 μm was collected.

The collected granules were then blended for 15 minutes, and the magnesium stearate was added and blending continued for a further 5 minutes. The blend was then compressed on a suitable tabletting machine using a 2mm tooling to produce rod-shaped implants of 2mm diameter and 5 mm length.

These implants were used in stability studies, in which the effects of BHA and electron beam irradiation were investigated. Implants containing 0.5% w/w BHA and having been treated at four different irradiation levels [control (0 kGy), 15 kGy, 20 kGy and 25 kGy] were stored at 30°C for 30 weeks, and then the percentage of doramectin remaining was determined. A control implant containing no BHA was also studied.

The results are shown in Figure 2. It can be seen that the presence of BHA dramatically improves the stability of the implants on storage, even when the implants have been irradiated.

**Claims:**

1. A solid implant comprising at least one parasiticidal compound having low aqueous solubility; and tabletting excipients including a bulking agent.

2. An implant as claimed in claim 1, which is adapted for subcutaneous implantation.

3. An implant as claimed in claim 1 or claim 2, wherein the parasiticidal compound has an aqueous solubility below 100 µg/ml.

4. An implant as claimed in claim 3, wherein the parasiticidal compound is an avermectin or a milbemycin.

5. An implant as claimed in claim 4, wherein the parasiticidal compound is doramectin.

6. An implant as claimed in any one of the preceding claims, wherein the bulking agent is lactose.

7. An implant as claimed in any one of the preceding claims, wherein the tabletting excipients include magnesium stearate.

8. An implant as claimed in any one of the preceding claims, wherein the tabletting excipients include a tablet disintegrant.

9. An implant as claimed in claim 8, wherein the tablet disintegrant is sodium starch glycolate.

10. An implant as claimed in any one of the preceding claims, which contains an antioxidant or a reducing agent.

11. An implant as claimed in claim 10, wherein the antioxidant is butylated hydroxy toluene or butylated hydroxy anisole.

12. An implant as claimed in any one of the preceding claims, which is sterilized by irradiation.

13. An implant as claimed in any one of the preceding claims, wherein the tabletting excipients include polyvinyl pyrrolidone.

14. An implant as claimed in any one of the preceding claims, wherein the parasiticidal compound makes up between 10 and 60% of the implant, by weight.

15. An implant as claimed in any one of the preceding claims, which is adapted for implantation into the ears of cattle or sheep.

16. An implant as claimed in any one of the preceding claims, which is rod-shaped.

17. A method for the treatment or prevention of parasitic infections which comprises administering an implant as defined in any one of claims 1-16 to an animal in need of such treatment.

18. Use of an antioxidant or a reducing agent in a formulation containing an avermectin or a milbemycin for preventing degradation of the avermectin or milbemycin.

19. The use as claimed in claim 18, wherein the formulation is irradiated.

20. The use as claimed in claim 18 or claim 19, wherein the formulation is not liquid.

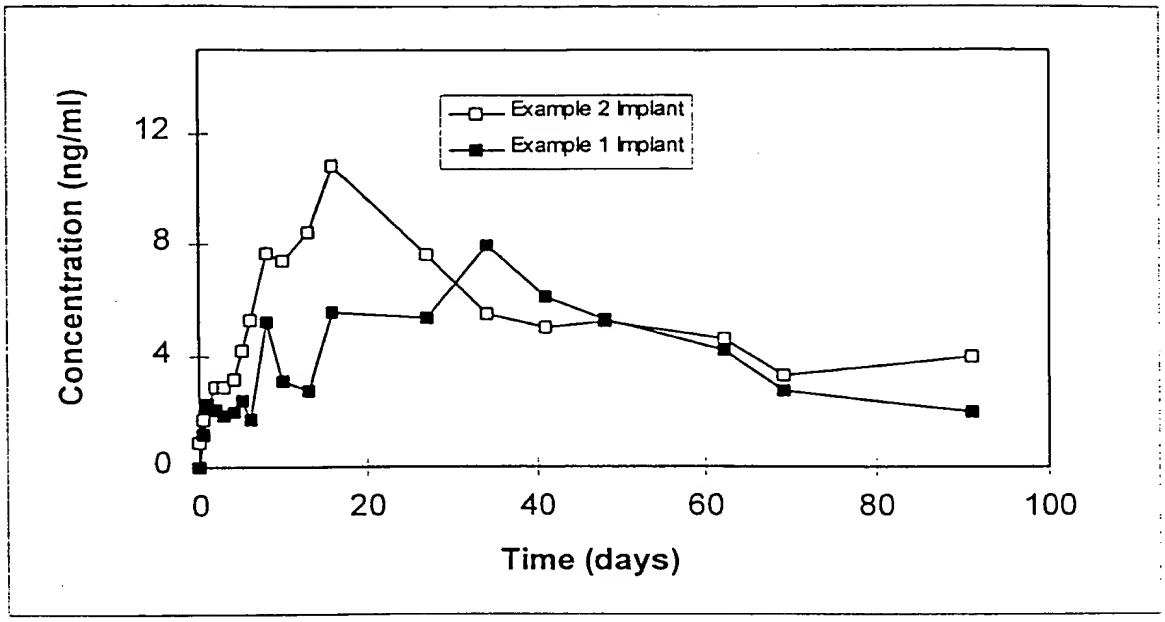

Example 2 Implant
Example 1 Implant
Concentration (ng/ml)
12
8
4
0
0
20
40
60
80
100
Time (days)

Figure 1

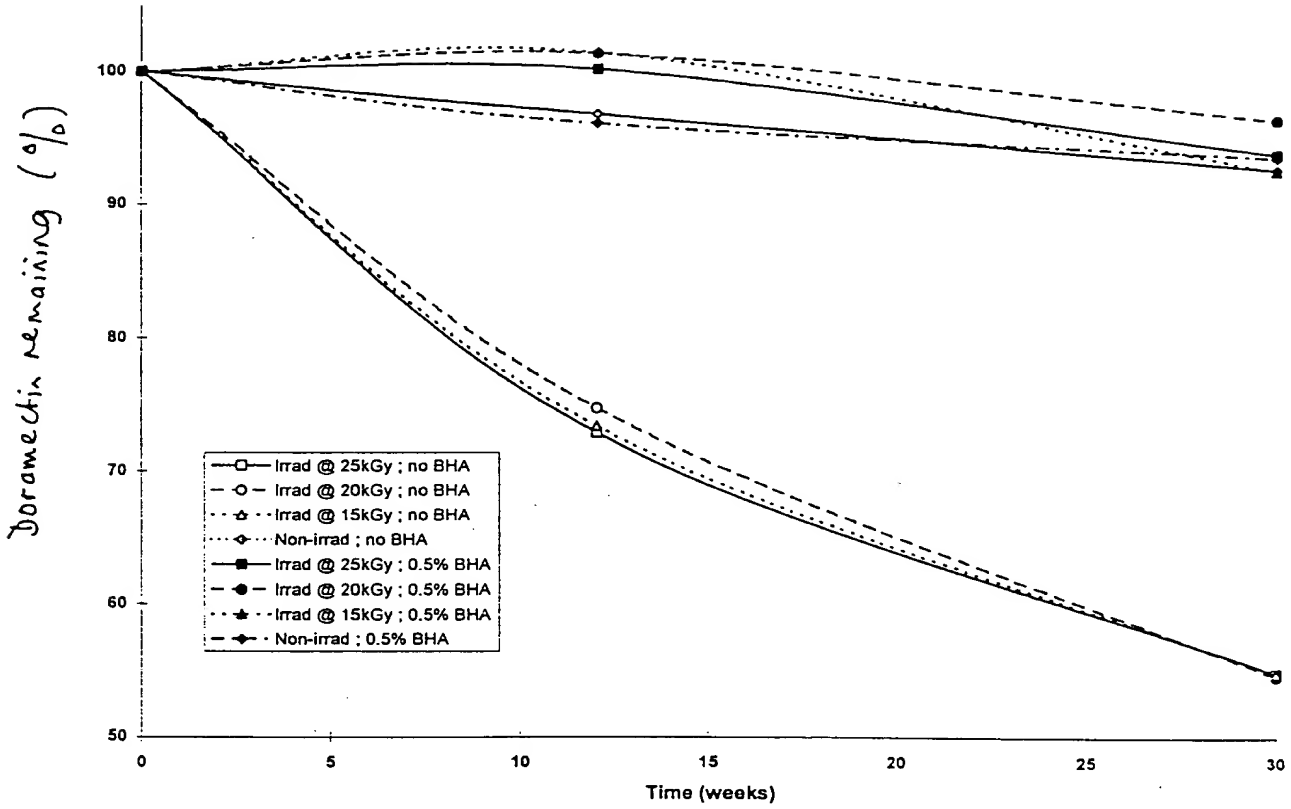

Doramectin remaining (%)
100
90
80
70
60
50
0
5
10
15
20
25
30
Time (weeks)
Irrad @ 25kGy ; no BHA
Irrad @ 20kGy ; no BHA
Irrad @ 15kGy ; no BHA
Non-irrad ; no BHA
Irrad @ 25kGy ; 0.5% BHA
Irrad @ 20kGy ; 0.5% BHA
Irrad @ 15kGy ; 0.5% BHA
Non-irrad ; 0.5% BHA

Figure 2